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Determination of nanomolar levels of perchlorate in water by ESI-FAIMS-MS

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Electrospray ionisation (ESI) was used to generate gas-phase anions that were subsequently separated by high-field asymmetric waveform ion mobility spectrometry (FAIMS) and detected by quadrupole mass spectrometry (MS). ESI-FAIMS-MS provided selective and sensitive determination of perchlorate at low nanomolar levels, relatively free from the interferences commonly observed for this analysis using conventional ESI-MS. In particular, the gas-phase separation of ions in FAIMS eliminated isobaric overlaps of bisulfate and dihydrogen phosphate with perchlorate. Using the FAIMS interface, analysis of 1 μM perchlorate in a 10 μM sulfate solution yielded a signal-to-background ratio (S/B) improvement of over four orders of magnitude (at *m/z* −99) compared with ESI-MS. The detection limit for perchlorate (in 9 : 1 methanol–water with 0.2 mM ammonium acetate and 10 μM sulfate) was 1 nM (≈0.1 ppb).

Introduction

Production and handling of perchlorate salts, related to their use as a solid oxidant in missiles, rockets and fireworks, have led to significant levels of perchlorate in the environment.[1] Elevated levels of perchlorate in drinking water have led to growing concerns regarding its toxicity. Perchlorate is a competitive inhibitor for iodide uptake in the human thyroid, hence the potential exists for the disruption of thyroid hormone production and homeostasis, possibly causing abnormal metabolism, growth and development.[1] Owing to the lack of sufficient toxicological data, perchlorate has been added to the US EPA's Drinking Water Contaminant Candidate List (CCL). In 1997, the California Department of Health Services (CA DHS) established a provisional action level for perchlorate in drinking water of 18 ppb.[1]

Only one method, based on ion chromatography (IC), has gained acceptance for trace analysis of perchlorate. The detection limits are about 0.3–0.7 ppb or about 3–7 nM, with a reporting limit of about 4 ppb.[2,3] This method relies on non-specific detection (*i.e.*, matching of the sample peak retention time with a standard peak), and the sample throughput is low owing to analysis times of the order of 10 min per sample. Other methods for measuring perchlorate with comparable detection limits are required to validate the IC method and to confirm results for difficult matrices. ESI-MS methods for perchlorate analysis have been reported with detection limits of about 50 nM.[4] However, this work was done in the absence of interfering matrix ions such as sulfate and phosphate. Recently, a method based on ESI-MS analysis of stable association complexes of perchlorate with organic cations was developed that achieves method detection limits of about 1 nM.[5]

A continuous flow technique for the separation of gas-phase ions at atmospheric pressure and room temperature, referred to as high-field asymmetric waveform ion mobility spectrometry (FAIMS), has been described.[6-8] This technique separates ions by taking advantage of the dependence of gas-phase ion mobility on applied electric field, E. At low electric fields, the ion mobility, K, is independent of field strength, whereas at high fields (*e.g.*, $E > 10^4$ V cm^{-1}) ion mobility is a function of E and may be denoted as K_h. If two ions have different values of K_h/K at a set electric field, FAIMS may be able to separate these two ions based on the difference in these values.[6]

The FAIMS analyser region, illustrated in Fig. 1, consists of two concentric cylinders; the outer cylinder is kept at a constant dc potential while an asymmetric waveform is applied to the inner cylinder. The waveform, $V(t)$, is composed of a brief high-voltage component and a longer low-voltage component of opposite polarity. The integrated voltage–time product of one complete cycle of the waveform is zero. The magnitude of the high-voltage component is referred to as the dispersion voltage (DV). Consider an ion (*e.g.*, perchlorate) that is transported by a gas stream between the two cylinders, as illustrated in Fig. 1. If the high-field portion of $V(t)$ is sufficiently large, such that $K_h > K$, the distance travelled by the ion during the high-field portion is greater than the distance travelled during the low-field portion of $V(t)$. The ion, therefore, experiences a net displacement from its original position during each cycle of $V(t)$, and begins to move toward the outer cylinder, as illustrated by the dashed line in Fig. 1.

To "compensate" for the drift of this ion toward the outer cylinder, a constant dc voltage is applied to the inner cylinder.

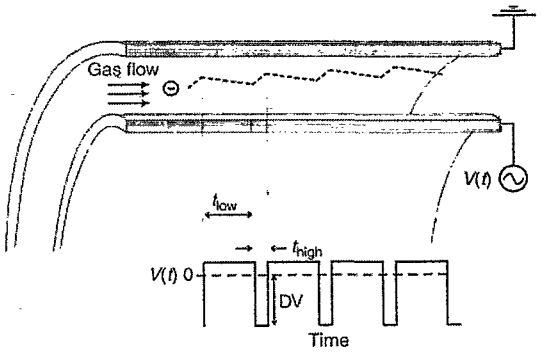

Fig. 1 Illustration of ion motion between the concentric cylinders of the FAIMS analyser during the application of an asymmetric waveform shown as $V(t)$; the ion is transported horizontally by a gas flow (distance not to scale).

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This dc voltage, referred to as the compensation voltage (CV), enables the ion to pass between the cylinders with no net drift towards either cylinder. If two ions (*e.g.*, perchlorate and bisulfate) respond differently to the applied electric field (*i.e.*, their ratios of K_h to K are not identical), the CV values necessary to prevent their drift will differ, allowing selective transmission of one ion over the other. To analyse a mixture of ions, the CV may be scanned to transmit each of the components of a mixture in turn, resulting in a CV spectrum.

Several applications of ESI-FAIMS-MS have recently been reported.[9–14] In this paper, the advantages of using FAIMS to separate ESI-generated perchlorate ions from bisulfate, dihydrogen phosphate, and other isobaric interferences, coupled with the selectivity and sensitivity of MS detection, are demonstrated.

Experimental

A schematic diagram of the ESI-FAIMS-MS instrument used in this study is shown in Fig. 2. A detailed description of this apparatus has been given previously.[7,8] Negative ions were produced with the electrospray needle biased at −2100 V, giving an electrospray current of about 40 nA. The DV of the asymmetric waveform applied to the long inner cylinder was varied between 0 and −3300 V. The frequency of the asymmetric waveform was 210 kHz. Since the spacing between the cylinders was 0.2 cm, the values of DV correspond to electric fields of roughly 0 to 16 500 V cm^{-1}. The CV, which was also applied to the long inner cylinder of the FAIMS analyser, could be scanned over specified voltage ranges, or set to a specific value to transmit selected ions. Note that slight differences in tuning the asymmetric waveform[15] might cause small day-to-day variations in the CV.

With appropriate DV and CV values, ions were transmitted through the FAIMS analyser and transferred through a 260 μm orifice plate to the vacuum chamber of a mass spectrometer [Perkin-Elmer SCIEX (Concord, ON, Canada) API 300 triple-quadrupole]. The MS orifice plate was electrically insulated from the FAIMS and a separate voltage (V_{OR}) of −39 V was applied to it. An offset voltage (V_F) of −49 V was applied to the entire FAIMS unit to enhance the sensitivity of the FAIMS–MS interface. These values of V_F and V_{OR} were optimised for transmission of perchlorate at DV = −3300 V. The skimmer cone was held at ground potential and the small ring electrode normally located behind the orifice of the API 300 was not incorporated into this design, probably resulting in some loss of sensitivity for low mass ions such as perchlorate. Compressed air was introduced into the carrier gas inlet (C_{in}) at a flow rate of 5 L min^{-1}. Gas exited through the carrier gas outlet (C_{out}) at 4 L min^{-1} and through the sample gas out port (S_{out}) at 1 L min^{-1}. The pressure inside the FAIMS analyser, which was measured with an MKS Baratron Type 170M-6B pressure meter (MKS Instruments, Burlington, MA, USA), was kept at approximately 785 Torr.

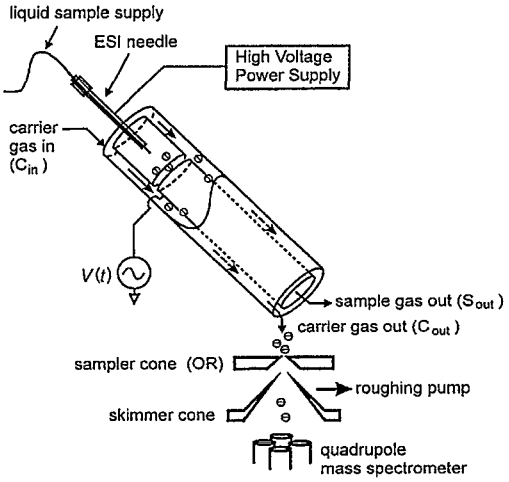

Fig. 2 Schematic diagram of the ESI-FAIMS-MS instrument.

Potassium perchlorate, potassium dihydrogen orthophosphate (J. T. Baker, Phillipsburg, NJ, USA) and potassium sulfate (Mallinkrodt, Montreal, QC, Canada) were used to prepare 0.01 M aqueous stock standard solutions, from which working standard solutions in 9 : 1 methanol–water containing 0.2 mM ammonium acetate (Anachemia, Montreal, QC, Canada) were made. Glass-distilled HPLC grade methanol (Anachemia) was used as received.

Results and discussion

ESI-MS

An ESI-MS spectrum of 10 μM sulfate with 0.2 mM ammonium acetate in 9 : 1 methanol–water is shown in Fig. 3(a). Intense peaks, including acetate (*m/z* −59) and oxalate (*m/z* −89), are present. In ESI-MS, sulfate appears as the bisulfate ion, HSO_4^-, with the major isotopomer at *m/z* −97.[16] The isotopes of sulfur and oxygen contribute to peaks at *m/z* −99 and −101. Fig. 3(b) is a magnified view of Fig. 3(a), which illustrates the complex nature of the ESI-MS background. Since ESI is a non-selective ionisation technique, many solution and gas-phase species (known and unknown) appear in the low mass region, contributing to the background interference.

ESI of a solution containing perchlorate yields intact perchlorate anions, *i.e.*, peaks at *m/z* −99 and −101 are observed in the mass spectrum. The presence of sulfate in

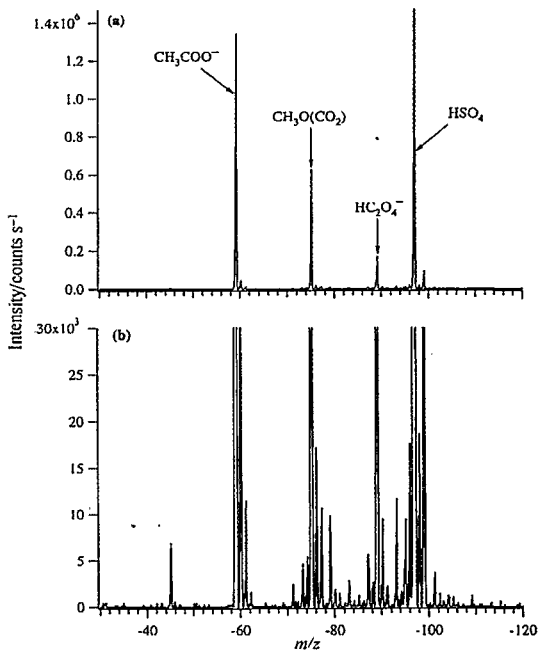

Fig. 3 (a) Mass spectrum of 10 μM sulfate in 0.2 mM ammonium acetate (9 : 1 methanol–water) acquired by conventional ESI-MS on an API 300 triple-quadrupole mass spectrometer; (b) expanded view of the spectrum in (a).

solution can interfere with trace-level determination of perchlorate, owing to the bisulfate isotopomers at m/z −99 and −101. Since sulfate is a common ion in groundwater and drinking water and an impurity in many types of chemicals, the direct determination of perchlorate is limited with ESI-MS. Other ions, such as phosphate, can also interfere with perchlorate determination. Phosphate can be observed as $H_2PO_4^-$ (m/z −97) in ESI-MS with a minor isotopomer (due to ^{18}O) at m/z −99. For simplicity, the phosphate interference will not be examined in detail.

Fig. 4(a) is an ESI-MS spectrum similar to Fig. 3(a) except that 1 μM perchlorate was added to the solution. Fig. 4(b) is an expanded view of Fig. 4(a), having the same absolute scale as Fig. 3(b). The peak at m/z −99 cannot be used for low level perchlorate quantification, largely owing to the isotopomer of bisulfate. At m/z −101, there is far less contribution from the bisulfate isotopomer, but the chemical background still limits reliable identification and quantitation of ClO_4^-.

ESI-FAIMS-MS

Ions are separated in FAIMS based on their differences in high *vs.* low field mobilities (*i.e.*, K_h/K). The effect of increasing E/N (where E is the electric field and N is the number density of the carrier gas) on K_h/K for both perchlorate and bisulfate is shown in Fig. 5. These experimentally determined curves correspond to dispersion voltages varying from 0 to −3300 V. The curves were determined by using eqn. (1):

$$CV+\alpha\left[\frac{(DV)^3}{9d^2}+\frac{15(CV)(DV)^2}{18d^2}+\frac{(CV)^3}{d^2}\right]+\beta\left[\frac{55(DV)^5}{486d^4}\right]=0 \quad (1)$$

where CV is the compensation voltage, DV is the dispersion voltage and the distance d between the inner and outer

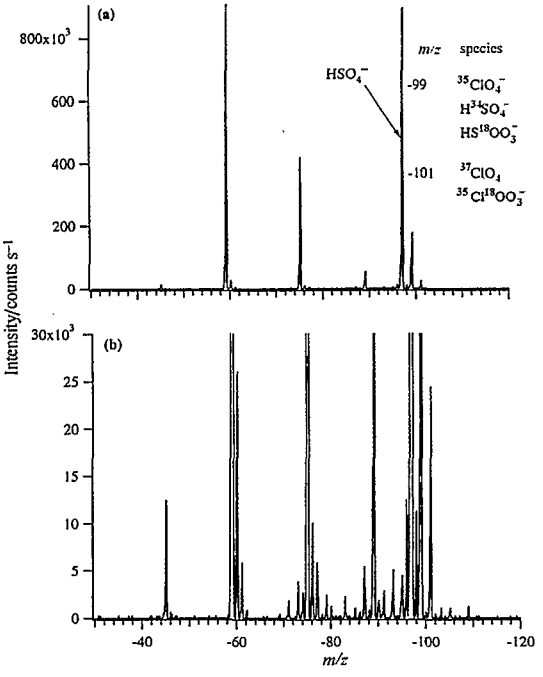

Fig. 4 (a) Mass spectrum of 1 μM perchlorate and 10 μM sulfate in 0.2 mM ammonium acetate (9:1 methanol–water) acquired by conventional ESI-MS on an API 300 triple-quadrupole mass spectrometer; (b) expanded view of the spectrum in (a).

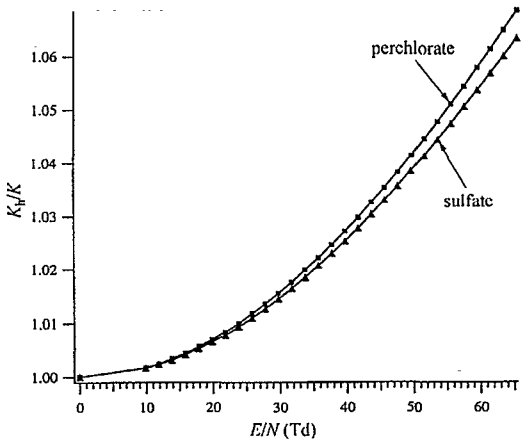

Fig. 5 Measured dependence of ion mobility (expressed as K_h/K) in air for perchlorate and bisulfate as a function of electric field strength within the FAIMS analyser (expressed as E/N, where N represents the gas number density).

cylinders was 0.2 cm, to determine the values of the high-field mobility parameters (α and β) as described elsewhere.[15] The values of α and β obtained from eqn. (1) (as a function of E) were converted to values expressed as a function of E/N, where E/N is in units of Td ($1\,Td = 10^{-21}\,Vm^2$). These new values of α and β were used to calculate K_h/K for each DV tested, according to the following equation:

$$\frac{K_h}{K}=1+\alpha\left(\frac{E}{N}\right)^2+\beta\left(\frac{E}{N}\right)^4 \quad (2)$$

Derivations of the equations describing the high-field behaviour of ions in a FAIMS device have been given elsewhere.[15] Fig. 5 shows that for these two ions, the difference in K_h/K continues to increase with increasing E/N to the maximum value tested (≈65 Td). The difference in the dependence of K_h/K on E/N for these two ions allows for their gas-phase separation at atmospheric pressure.

The ability of FAIMS to separate and focus perchlorate and bisulfate ions is demonstrated in Fig. 6. In each trace, the voltage of the asymmetric waveform was set, and ion-selected

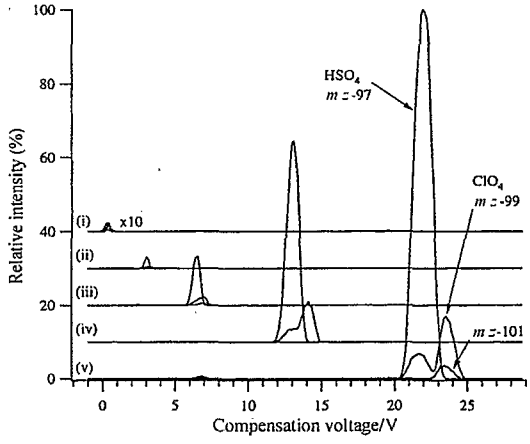

Fig. 6 IS-CV spectra (m/z −97, −99 and −101; CV = −1 to 29 V; DV = −3300 V) of 1 μM perchlorate and 10 μM sulfate in 0.2 mM ammonium acetate (9:1 methanol–water). DV = (i) 0, (shown magnified 10× for clarity), (ii) −1600, (iii) −2100, (iv) −2700 and (v) −3300 V.

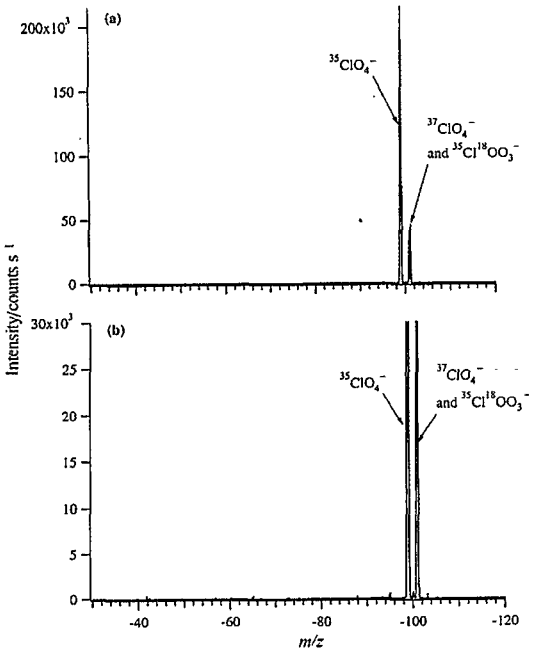

Fig. 7 (a) Mass spectrum of a solution containing 1 μM perchlorate and 10 μM sulfate in 0.2 mM ammonium acetate (9 : 1 methanol–water) at DV = −3300 V and CV = 23.6 V; (b) expanded view of the spectra in (a).

CV spectra (IS-CV) were acquired at *m/z* −97, −99 and −101 with the CV scanned from −1 to +29 V. The trace for *m/z* −97 represents the major isotopomer of HSO_4^-, and those for *m/z* −99 and −101 represent minor isotopomers of HSO_4^- and the two major isotopomers of ClO_4^-. The dwell time and number of scans were kept constant for each spectrum. At DV = 0 V [trace (i)], the ions all appear at a compensation voltage near 0 V. The IS-CV spectrum acquired at DV = −1600 V is shown in trace (ii). The transmitted ions have experienced small, field-induced increases in their mobility at this DV and therefore appear in the spectrum at CV values >0 V. As the DV was made more negative, the species were transmitted at more positive CV values as shown in traces (iii)–(v). These shifts to more positive CV values are accompanied by increases in the measured ion intensity, a consequence of two-dimensional focusing within the FAIMS analyser.[7] At DV = −3300 V [trace (v)], the perchlorate ion (at *m/z* −99) has experienced an increase in sensitivity of about three orders of magnitude compared with the trace at DV = 0 V. At DV = −3300 V, sulfate (*m/z* −97) appears at a CV value of 21.9 V and perchlorate (*m/z* −99) is transmitted at a CV of 23.6 V. This DV (−3300 V), which is the highest voltage that could be applied with this FAIMS apparatus, provides the largest separation of these ions.

To illustrate the improvement in the mass spectral background achieved using FAIMS, a mass spectrum was acquired by tuning the FAIMS to DV = −3300 V and CV = 23.6 V. This mass spectrum, shown in Fig. 7(a) and (b), was acquired for a solution of 10 μM sulfate and 1 μM perchlorate. In Fig. 7(b), the vertical axis has been expanded to the same number of absolute counts as done previously for Fig. 4(b). A comparison of these expanded spectra shows that the filtering action of the FAIMS analyser has significantly reduced the chemical background. Since the signal intensity at this DV is comparable to that in conventional ESI-MS, significant improvements in the signal-to-background ratio (S/B) are achieved using the FAIMS interface. Comparing the ESI-MS signals observed for a 10 μM sulfate "blank" solution and a solution containing 1 μM perchlorate and 10 μM sulfate, the S/B for perchlorate was 2.0 and 6.6 for *m/z* −99 and −101, respectively. An analysis of the same solutions using ESI-FAIMS-MS (DV = −3300 V and CV = 23.6 V) results in S/B at *m/z* −99 and −101 of 72 000 and 15 000, respectively. This dramatic improvement in S/B provides low perchlorate detection limits in the presence of sulfate, without ancillary sample preparation or tandem mass spectrometry (MS/MS).

The ability of FAIMS to separate perchlorate and bisulfate is not compromised as the sulfate concentration is increased or as the perchlorate concentration is decreased. This is demonstrated in Fig. 8(a) and (b), which show IS-CV spectra of 0.1 μM perchlorate in the presence of 50 μM sulfate and 50 μM phosphate. This represents a 10-fold decrease in the perchlorate concentration, a 5-fold increase in the sulfate concentration and the addition of phosphate compared with the test solution used in Fig. 6 and 7. The expanded view illustrates the potential interference on the perchlorate analysis due to dihydrogen phosphate at *m/z* −99 and due to bisulfate at *m/z* −97 and −101. The figure shows that these interferents can be readily separated from the perchlorate signal. Consequently, FAIMS allows for the monitoring of perchlorate at a specific CV, over a wide range of sulfate and phosphate concentrations. The mass spectrum at CV = 24.2 V [Fig. 8(c)] shows the signal for the perchlorate ion (0.1 μM) with minimal background ion intensity.

A standard response curve for perchlorate in the presence of 10 μM sulfate (with 0.2 mM ammonium acetate in 9 : 1 methanol–water as solvent) was established. The sample was continuously electrosprayed into the FAIMS analyser and perchlorate (*m/z* −99) was monitored at DV = −3300 V and CV = 24.2 V. The dwell time was 300 ms and 30 integrations were averaged for each measurement. Six solutions, ranging in concentration of perchlorate from 0.01 to 1 μM, were analysed. The response was linear over this concentration range described by the equation $y = 9450[ClO_4^-] + 1.4$ ($r^2 = 0.9989$). The detection limit for perchlorate in 9 : 1 methanol–water with

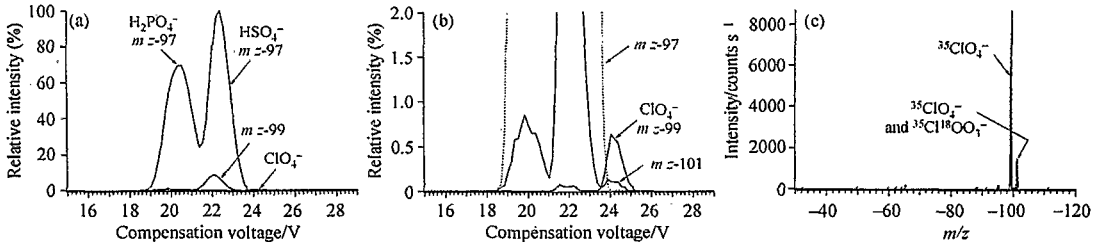

Fig. 8 (a) IS-CV spectra (*m/z* −97, −99 and −101; CV = 15–29 V; DV = −3300 V) of 0.1 μM perchlorate, 50 μM sulfate and 50 μM phosphate in 0.2 mM ammonium acetate (9 : 1 methanol–water); (b) expanded view of (a) with *m/z* −97 shown as a dashed line for clarity; (c) mass spectrum of the same solution at CV = 24.2 V.

0.2 mM ammonium acetate and 10 μM sulfate was 1 nM (≈0.1 ppb). This value was calculated based on three times the standard deviation of the blank (10 μM sulfate in 0.2 mM ammonium acetate in 9 : 1 methanol–water).

Conclusions

The differences in K_h/K of perchlorate, bisulfate and dihydrogen phosphate ions allow FAIMS to separate them in the gas phase at atmospheric pressure prior to their introduction into a mass spectrometer. The filtering action of FAIMS results in a dramatic decrease in the background, and its focusing action provides a signal intensity that is comparable to that in ESI-MS. Consequently, ESI-FAIMS-MS significantly improves the detection limit of perchlorate when compared with ESI-MS.

Relatively high concentrations of sulfate and phosphate were shown not to compromise the separation of perchlorate from these potentially interfering ions. Hence, even in the presence of variable amounts of sulfate and phosphate in the matrix, the FAIMS voltages can be tuned to transmit perchlorate continuously without interference.

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